

**REMARKS**

**Status of the Claims**

Claims 1-20 are pending in the Application. Claims 1-12 are currently rejected. Claims 1, 3, 4, 5, 6, 8, 9, and 10-12 are currently amended. New claims 13-20 are added by this amendment. Reconsideration and allowance of all of the pending claims is respectfully requested.

No new matter is being added to the Application by way of this amendment. Support for the amendment to claims 1, 3-5, 8, and 10-12 may be found for example at page 6, line 2 of the Specification.

The amendments to claims 4 and 6 delete references to the terms intra-ocular, oral, dermal, and ocular.

New claims 13 to 20 are supported at pages 5-6 of the Specification.

Accordingly, entry of this amendment is appropriate and respectfully requested.

**Claim Rejections – 35 U.S.C. §102 (pages 2-3 of the Office Action)**

*1. Kaswan*

Claims 1, 2, 4 and 6 are rejected under 35 U.S.C. §102(b) as anticipated by Kaswan (U.S. Patent No. 4,649,047). The Applicants respectfully traverse this rejection for the following reasons.

Kaswan discloses a method of treating eye disorders via the topical application of cyclosporin in a concentration of 0.1 to 20 wt % in a medically suitable excipient. Kaswan lists over 15 possible excipients, which include dimethyl sulfoxide (DMSO) and olive oil. Kaswan clearly describes that the cyclosporin is “topically administered as an ophthalmic drop or

ophthalmic ointment." See Col. 6, lines 42-44. Further, Kaswan limits the total quantity of such cyclosporin ophthalmic drop or ophthalmic ointment "within the range of 5 microliters to 1 milliliter." See Col. 6, lines 49-51.

In reply to the Examiner's mention of Example 2, it is submitted that after careful examination of all of the given Examples 1 to 4, Kaswan fails to reveal any reference to DMSO. See Cols. 7, 8, 9, 10 and 11. There are numerous references (beyond Example 2) to olive oil as the vehicle for 2% cyclosporin delivered either by mouth (per os) or as eye drops "15  $\mu$ liters of 2% cyclosporin in olive oil applied topically" (Example 1: Col. 7, lines 64-70, Col. 8, lines 1-5); "1% tritiated cyclosporin in oil was applied to the eyes" (Example 3: Col. 9, line 44-64); "The other rabbits received 10 micoliters of 2% cyclosporin in olive oil applied topically to both eyes" (Example 4: Col. 10, line 14-43) and "8 rabbits which received 10 micoliters of cyclosporin (Sandimmune $\circledR$ ), 2% in olive oil applied to the dorsal limbus" (Example 4: Col. 11, line 19-28).

Certainly, DMSO is not a preferred excipient of Kaswan since it is never used in the Examples of cyclosporin ophthalmic solutions, and instead exclusively an olive oil 2% cyclosporin fluid is used. Kaswan claims 7, 8, 13 and 14 are dependent claims where DMSO is one of, or the excipient, for cyclosporin for ophthalmic topical application to the eye. Kaswan claims 3 and 4 are dependent claims that give a cyclosporin content of 0.1 to 50 wt % of the ophthalmic eye drops. The reference to eye drop compositions is not related to cyclosporin concentrations beyond ophthalmic eye drop compositions, and therefore is not relevant to the instant claims. Instant claim 1 excludes ophthalmic eye drop compositions, and further recites that the present compositions are "not intended for ophthalmic, cutaneous, oral or gavage application". Claim 1 is thus novel over Kaswan.

Claim 2 is dependent on claim 1 and is novel for at least the same reason.

Claim 4 is novel over Kaswan at least in view of "a sterile injectable solution" and the now excluded "intra-ocular" administration.

Claim 6 is novel over Kaswan since inhalation or nasal administration, as required by claim 6, is not disclosed in Kaswan and in view of the exclusion of reference to "oral, dermal or ocular" administration.

Accordingly, withdrawal of this rejection is respectfully requested.

*2. Elzinga*

Claims 1, 2 and 6 are rejected under 35 U.S.C. §102(b) as anticipated by Elzinga et al. (Transplantation, vol. 47, No. 2, pp. 394-395, February 1989). The Applicants respectfully traverse this rejection for the following reasons.

Elzinga discloses an oral or gavage formula for cyclosporin in DMSO at a concentration of 15 mg/ml. Elzinga et al. in no way suggest that a DMSO and cyclosporin formula be used by any other composition other than oral. The present claims have been amended to specify that the solution is "a sterile injectable solution" and is "not intended for ophthalmic, cutaneous, oral or gavage application" (claims 1 and 2), or have been limited to inhalation or nasal application thus removing reference to "oral, dermal or ocular" compositions (claim 6). Claims 1, 2 and 6 as amended are thus novel over Elzinga et al.

Withdrawal of this rejection is respectfully requested.

**Claim Rejections – 35 U.S.C. §103 (pages 3-8 of the Office Action)**

Claims 1-12 are rejected under 35 U.S.C. §103(a) as unpatentable over Kaswan taken with Elzinga et al. (Transplantation, vol. 47, No. 2, pp. 394-395, February 1989), Broadwell et al. (Science, vol. 217, No. 4555, pp. 164-166, July 9, 1982) and Elias (U.S. Patent No. 5,807,820). The Applicants respectfully traverse this rejection for the following reasons.

The Examiner notes that Kaswan teaches that cyclosporin in DMSO can be topically administered to the eyes as an ophthalmic solution. The Examiner confirms that this differs from

previous claims 3, 5 and 7 to 12 in the routes of administration, the description of packaging material and formulation, and method of treating neurodegenerative and neurological diseases, and inducing systemic immunosuppression for transplantation and autoimmune disease.

The Examiner invokes the Elzinga et al. reference where cyclosporin in DMSO is administered by gavage to rats. The Examiner notes the increased blood levels of cyclosporin when administered with DMSO into the stomach. The Examiner notes that DMSO is an excellent organic solvent that readily penetrates most tissue membranes, acting as a “carrier” for many solutes, including various drugs.

The Examiner concludes: “Thus, the reference clearly shows that DMSO penetrates most biological membranes with ease, and has been used as an effective carrier of drugs and other solutes and considered to be safe.” See Office Action, page 5.

The Examiner goes on to assert: “Complete pharmacokinetic and immunosuppression studies in humans are warranted as the use of DMSO as the vehicle for CsA could result in considerable cost savings, provided immunosuppression is not compromised”. See Office Action, pages 5-6, bridge paragraph.

Elzinga showing that DMSO as a carrier may or may not have an enhanced effect carrying oral CsA across the intestine into the blood has no relevance or interest to methods (or compositions) that are not to oral administration, especially in relation to administration into the blood or cerebrospinal fluid, with no membranes that need to be crossed to get into the blood to induce immunosuppression. This potential membrane crossing effect has no relevance to methods (or compositions) that are not for oral administration, since there are no membranes or barriers of any kind, nor the blood brain barrier, to cross in such applications.

While DMSO may be an effective carrier of drugs in vitro and in the laboratory, contrary to the assertion of the Examiner, DMSO is not used in this way in humans. Indeed, to the best of the Applicant's knowledge, there was not one single drug formula in the United States Pharmacopeia that uses DMSO as a drug carrier, at the time of the instant application on

February 26, 1999. Clearly, average practitioners of the art at the time had no teaching or suggestion to use DMSO as a solvent in any human drug formula, further evidencing the non-obviousness of the instantly claimed invention.

The Examiner asserts that DMSO is "considered to be safe" (p. 5 of the Action, four lines from bottom). This is not the case, when taken in full context, as demonstrated from the following examples and quotes from the art cited in the Office Action.

The Examiner extracts the sentences from Broadwell that indicate that DMSO might be safe, and overlooks the adjacent sentences with evidence for alarming DMSO toxicity at moderate doses. In particular, the Examiner asserts: "Regardless of the volume, concentration and route of delivery of DMSO, the corneas, lungs, heart, kidneys, liver and intestines of all DMSO injected mice appeared normal on gross examination at autopsy." See page 6, lines 11-13, of the Office Action.

However, Broadwell also states: "All mice given DMSO intravenously exhibited brief hind-limb muscle twitching and hematuria." See page 164, Col. 3, last paragraph. This finding suggests neurological injury, possibly seizures, and enough kidney or bladder damage to cause bleeding into the urine, in all of the animals given DMSO by an intravenous route. This would not be considered evidence of safety, and is in fact evidence of toxicity.

Further, the Examiner states: "Brains and pituitaries from animals given 0.5 ml of DMSO intraperitoneally and 0.25 ml of DMSO intravenously at concentrations up to 15% did not exhibit hemorrhage." See page 6, lines 8-10 of the Office Action. However, Broadwell also discloses results of slightly higher doses of DMSO and states:

Intraperitoneal injection of 0.5 to 1 ml of 20 to 30 percent DMSO coupled with a 0.25-ml intravenous injection of DMSO at the same concentration was tolerated by the animals; however, many exhibited anterior pituitary and superficial cortical hemorrhages and poorly preserved cell and organelle membranes.

See Broadwell, page 165, Col. 1, first paragraph. Brain hemorrhage is a serious brain injury. Damage to the brain cortex in the form of surface hemorrhages (“superficial cortical hemorrhages”) cannot be considered a mild injury, or safe.

Bleeding into the pituitary gland, the master hormone gland at the base of the brain can cause serious hormone, fluid and electrolyte balance irregularities and possible blindness from compression of the adjacent optic chiasm. Thus, pituitary gland hemorrhages cannot be considered mild injury, or evidence of safety.

That cell and subcellular organelle membranes were “poorly preserved” suggests a significant generalized toxic effect of DMSO. Thus, the Office Action neglects clear evidence of significant toxicity in the cited art just adjacent to the sentences selected to give the impression of safety.

The next reference cited in the Office Action is Elias. Elias makes no reference to safety or toxicity of DMSO, but only uses DMSO in *in vitro* studies, and does not administer DMSO to living whole organisms in the Examples of either living mice or humans. That Elias does not use DMSO in living organisms (but does use other solvents in live animals in humans) strongly suggests that DMSO would not be used as a pharmaceutical solvent by a practitioner of the art.

The next paper cited by the Examiner is Elzinga. While the Examiner cites the phrase that DMSO is “considered to be safe”, the Office Action omits reference to the second part of the same sentence that points out the known DMSO toxicity. Elzinga discloses:

While generally considered to be safe, toxicity studies in animals have demonstrated changes in the refractive index of the lens during chronic administration (14). Although such an effect has not been observed in humans (14), appropriate caution in the clinical application of DMSO has ensued.

See Elzinga, page. 394, Col. 2, next to last paragraph. Despite publishing papers on cyclosporin through from 1989 to 2000, a PubMed search using the keywords “Elzinga lw and

DMSO” shows no further reference to DMSO after this Brief Communication in Transplantation in 1989. This suggests that it was not warranted to attempt using DMSO as an excipient for oral cyclosporin. The Office Action selectively cites that DMSO is considered to be safe, but fails to mention that in the very next sentence there is a warning of cataract formation (changes in the refractive index of the lens), and the observation that the art of the day taught that ”appropriate caution in the clinical application of DMSO has ensued.” Thus, none of the art cited in the Office Action suggests that DMSO is safe, and indeed contains ample warnings to its toxicity. Thus the average practitioner of the art would be taught away from considering DMSO as part of a pharmaceutical formula for humans based on prior art teachings.

Further, in the Applicant's Information Disclosure Statement (IDS) of November 1, 2005, which was considered by the Examiner, is the reference: “Shimizu et al. Dimethylsulfoxide (DMSO) treatment reduces infarction volume after permanent focal cerebral ischemia in rats, Neuroscience Letters, Vol 239, No. 2-3, December 19, 1997, pp. 125-127.”

The Office Action does not cite Shimizu. Shimizu describes how DMSO is sometimes used as a vehicle for drugs in animal experiments of ischemia. This article is purely about DMSO and its effects, and not as a carrier of any drug. Shimizu makes no mention whatsoever of cyclosporin. Shimizu shows that DMSO itself may reduce brain infarction in stroke models in rats, on a background of conflicting reports in the literature. See page 126, Col. 2, paragraph 2 and 3.

Shimizu documents that in 1997, the average practitioner of the art would know that DMSO was generally considered unsafe for human use, even if 20 years before that (i.e. 1977) it was in popular usage by the lay community (i.e. not prescribed by physicians) for topical application to treat arthritis. Shimizu states:

The human use of DMSO was popular two decades ago when the compound was used for many inflammatory disorders. Clinical trials have suggested that it was as effective in the treatment of intracranial hypertension in brain trauma patients, but may produce significant side effects including fluid and electrolyte disorders [9,19]. Since the compound

is a readily available chemical, it was widely used without prescription for treatment of inflammatory disorders. However, it became apparent that DMSO may be toxic especially when used chronically: DMSO may produce many side effects for [sic] local skin irritation to intravascular hemolysis [7]. Accordingly, its human use has been curtailed." (P. 126, Col. 2, paragraph 4)

Thus, Shimizu et al clearly teaches that the practitioners of the art had curtailed the human use of DMSO by 1997, because of its toxicities including fluid and electrolyte disorders, local skin irritation and intravascular hemolysis and would not consider it safe as part of a pharmaceutical formula for humans. The Applicants respectfully submit that the Examiner has not adequately considered Shimizu in making the assessment of the perceived safety of DMSO.

Thus, Elzinga, Broadwell, Elias and Shimizu, separately, and together, would convince the average practitioner of the art that there are significant toxicity and safety concerns regarding DMSO that would teach one skilled in the art away from considering its use in a formula designed for nasal or inhalational administration, or for injection into the blood or cerebrospinal fluid. The disclosed risks include especially intravascular hemolysis (red blood cell breakdown in the arteries and veins), superficial brain hemorrhages, fluid and electrolyte abnormalities, cell and organelle membrane alterations, pituitary gland hemorrhages, hematuria (bleeding into the urine), hindlimb twitching and cataract formation. Thus, the average practitioner of the art would be taught away from using this toxic solvent in an intravenous or cerebrospinal pharmaceutical formula, thus demonstrating the unobviousness of the instant invention.

Elias discloses cyclosporin compositions suitable for dermal application only, and does not disclose cyclosporin compositions suitable for administration into the blood or cerebrospinal fluid, nasally, or inhalationaly. See Abstract. Further, the entire set of Elias claims 1-7 make no mention of DMSO, although they do mention 24 other suitable excipients. (Col. 13, lines 14-20 and Col. 14, lines 1-18)

In Elias, the only use of DMSO is in an *in vitro* test composition, as described below. Thus Elias fails to describe a DMSO and cyclosporin medicinal formulation.

The Elias Example 8 describes an *in vitro* test that takes a specimen of surgically excised skin from a hairless rat which is placed on a laboratory apparatus pictured in Fig. 1. The complex test apparatus function is briefly described, with input and output ports, and utilizes fluids containing methanol and radioactive tritiated-cyclosporins to measure how much cyclosporin is able to cross the specimen of hairless rat skin sample in the device. Various “test compositions” containing cyclosporin and excipients are employed, with a total of 6 test compositions described. The first 3 compositions include cyclosporin and ethanol. Test composition A.3 includes DMSO: “A.3. 20% Ciclosporin+80% ethanol/DMSO (70:30 p.p.w).” See col. 9, line 36-37. Elias clearly states that DMSO is used only for its function as a skin penetration enhancer. “NOTE: Composition A.2 and A.3 comprise conventional skin-penetration enhancers azone, and DMSO (dimethyl sulfoxide).” Col. 9, line 46-48.

Elias further notes that A.3 is an inferior delivery formula. “Composition B.1 and B.2 in accordance with the invention thus exhibit markedly and surprisingly improved delivery through the cornea and specifically, to the skin, than any of compositions A.1 to A.4.” See col. 10, line 13-16.

Composition A.3 is used only in the *in vitro* skin sample apparatus study, but is not used in the later *in vivo* live hairless rat study of Example 10 (Col. 11, line 30-44), nor in the human clinical trial application to the skin of psoriasis patients of Example 11 (Col. 12, line 8-10).

Thus Elias teaches that DMSO is suitable only for an *in vitro* apparatus excised skin sample “test composition”, and is not suitable for *in vivo* or human use as a topical excipient. Further Elias teaches that DMSO, even as a skin-penetration enhancer produces inferior penetration of cyclosporin into the skin. Thus Elias, either alone or in combination with other references would not encourage the average practitioner of the art to employ DMSO even in a dermal formula, much less a formula for administration into the blood or cerebrospinal fluid, nasally, or inhalationally.

While Elias discloses several topical formulas having a composition from 0.1 to 50% of cyclosporin in the claims 1 and 2, none of these formulas contain DMSO.

In view of the clear evidence of toxicity and a lack of any disclosure of the prior use of DMSO as a solvent for nasal, inhalation, or administration into the blood or cerebrospinal fluid for a pharmaceutical containing cyclosporin, one of skill in the art would not have been led directly and without difficulty to the instantly claimed invention. Accordingly, withdrawal of this rejection is respectfully requested.

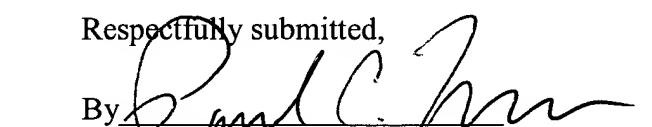
The Applicant affirms that all subject matter instantly claimed was commonly owned by both inventors to address the Examiner's comment in the first full paragraph of page 4 of the Action.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell (Reg. No. 36,623) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

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Respectfully submitted,

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